CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

METIRAM

Chemical Code # 493, Tolerance # 217
SB 950 # 63

September 12, 1991

I. DATA GAP STATUS

Chronic toxicity, rat: Data gap, inadequate study, possible adverse effect indicated.

Chronic toxicity, monkey: Data gap, inadequate study, possible adverse effect indicated.

Oncogenicity, rat: Data gap, inadequate study, no adverse effect indicated.

Oncogenicity, mouse: Data gap, inadequate study, possible adverse effect indicated.

Reproduction, rat: Data gap, inadequate studies, no adverse effect indicated.

Teratology, rat: Data gap, inadequate studies, possible adverse effect indicated.

Teratology, rabbit:	Data gap, no study on file.
Gene mutation:	No data gap, no adverse effect.
Chromosome effects:	Data gap, inadequate study, possible adverse effect indicated
DNA damage:	No data gap, possible adverse effect.
Neurotoxicity:	Not required at this time.

All record numbers through 900001 and 048606 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T910912
Prepared by H. Green and S. Morris, 09/12/91.

NOTE: EPA's "Guidance for the Reregistration of Pesticide Products Containing Metiram as the Active Ingredient" was published October 1988.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

217-015 036234, "Metiram Toxicity and Tumorigenicity in Prolonged Dietary Administration to the Rat" (Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, Report # BSF 199/7915 and BSF 199/80391, 5/7/81). Metiram of unstated purity with 2% ETU added was fed in the diet of 80 rats / sex / group for 111 (females) or 119 (males) weeks at 0, 5, 20, 80, or 320 ppm. A **possible adverse effect** was indicated by skeletal muscle atrophy in both sexes at 320 ppm (NOEL = 80 ppm). The study was unacceptable and not upgradeable because of no purity analysis and inadequate histopathology and dose justification (C. Aldous, 11/19/85).

217-002 006412, Summary of 036234.

217-004 006414, Interim report of 036234.

217-012 036229, Duplicate of 006414.

217-015 036235,
036236, Appendices of 036324.

217-016 036237,
036238, Appendices of 036324.

Note: The possible adverse effect indicated is listed in the rat chronic toxicity data gap status and not the rat oncogenicity data gap status.

CHRONIC TOXICITY, RAT

See Combined, Rat above and the supplemental 13-week study in rats below (doc. # 217-003, rec. # 006413).

CHRONIC TOXICITY, DOG

No study on file.

CHRONIC TOXICITY, MONKEY

217-006 006416, Rodney J. Sortwell et al., "Metiram (Containing 2.2% Ethylenethiourea) Oral Toxicity Study in Rhesus Monkeys", BSF 267/78263, Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, 1/15/79. Suspensions of metiram of unspecified purity with 2.2% ethylenethiourea were given by oral gavage once a day, seven days a week for 26 weeks to 4 rhesus monkeys / sex / group at 0, 5, 15, or 75 mg/kg/day. One animal / sex / group were allowed to recover for 15 weeks. A **possible adverse** effect was indicated by treatment-related decreases in serum T3 and T4 levels and thyroid hyperplasia seen in the main treatment and recovery groups in both sexes at 15 and 75 mg/kg/day. The study was unacceptable and not upgradeable because of insufficient numbers of animals and duration of dosing (J. Wong, 4/1/85; S. Morris, 3/6/91).

217-006 006416, Rodney J. Sortwell et al., "Investigation of Thyroid Function by Assessing the Uptake of Radiolabeled Iodine (^{131}I) Following Repeated Oral Administration of Metiram (Containing 2.2% Ethylenethiourea)", Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, 1/15/79. Suspensions of metiram of unspecified purity with 2.2% ethylenethiourea were given by oral gavage once a day, seven days a week for 27 weeks to 2 rhesus monkeys / sex / group at 0, 5, or 75 mg/kg/day. Radiometric assays were used to measure thyroid functions after iv injections of ^{131}I on weeks -11, -2, 1, 4, 8, 16, and 27. A possible **adverse effect** was indicated by protein-bound serum iodine being increased at 27 weeks in the high dose

group and dose-related, transient decreases in thyroid iodine accumulation followed by increases to above-normal values at the end of the study. The study was unacceptable and not upgradeable because of insufficient numbers of animals and duration of dosing (J. Wong, 4/1/85; S. Morris, 3/6/91).

217-002 006410, Summary of 006416.

217-012 036230, Duplicate of 006416.

Note: The supplemental monkey studies are included here because there is no adequate non-rodent study on file and a possible adverse effect is indicated.

ONCOGENICITY, RAT

See Combined, Rat above.

ONCOGENICITY, MOUSE

217-014 036232, "Metiram Tumorigenicity to Mice in Long Term Dietary Administration (Final Report) Part I", (Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, Report # BSF 198/78265, 6/5/79). Metiram of unstated purity with 2% ETU added was fed in the diet for 88 to 96 weeks to 52 mice / sex / group at 0, 100, 300, and 1000 ppm. A **possible adverse effect** was indicated by a treatment-related increase in benign liver cell tumors in males at 1000 ppm. The study was unacceptable and not upgradeable because of insufficient histopathology, no purity analysis, lack of blood data, and no dose level justification (C. Aldous, 11/18/85).

217-014 036233, Appendices for 036232.

217-007 006417, Duplicate of 036232.

217-008 006418, Duplicate of 036233.

REPRODUCTION, RAT

217-013 036231, "Effect of Metiram Technical on Reproductive Function of Multiple Generations in the Rat" (Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, Report # 200/80692, 3/18/81). Metiram technical of unstated purity with 2% ETU added was fed in the diet for three generations (2 litters / generation) at nominal concentrations of 0, 5, 40, and 320 ppm. There were 12 male and 24 female rats / parental group. There were no treatment-related effects reported. No adverse effects were indicated. The study is unacceptable and not upgradeable because of inadequate toxicity at the highest dose (C. Aldous, 11/14/85).

217-002 006411, Summary of 036231.

217-005 006415
217-011 036228, Interim F2 generation data for 036231.

217-001 900000
900001, Invalid IBT study.

TERATOLOGY, RAT

217-011 036227, Anthony K. Palmer and Rona Simons, "Effect of Metiram Technical on Pregnancy of the Rat" (Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, Report # BSF 302/79616, 8/3/79). Metiram technical of unstated purity with 2% ETU added was administered by gavage to 20 pregnant female rats / dose on gestation days 6 thru 15 at 0, 40, 80, or 160 mg/kg/day. There were no significant treatment-related maternal effects. A **possible adverse**

effect was indicted by decreased live litter size at 160 mg/kg/day (NOAEL = 80 mg/kg/day). Unacceptable but possibly upgradeable with submission of test article analysis, dosing solution stability, clinical observation data, and adequate rationale of dose (C. Aldous, 11/13/85; S. Morris, 2/28/91).

TERATOLOGY, RABBIT

No study on file.

GENE MUTATION

217-011 036225, "Ames Test for Metiram" (Institute of Pharmacology, University of Mainz, Germany, 8/22/77). Metiram of uncertain purity (DMSO solvent) was used in the Ames reverse mutation assay. Σαλμονελλα τψπηιμυριυμ strains TA98, TA100, and TA1537 were treated in duplicate with and without activation (S9 fraction from Aroclor-induced male Sprague-Dawley rat liver homogenates) at 0 (no DMSO), 0, 3.1, 10.0, 31.0, 100.0, 310.0, 1000.0, and 2000.0 µg/plate. There were no compound-related increases in reversion rates. The study is unacceptable and not upgradeable because there were only 3 tester strains (J. Gee, 11/22/85).

** 217-011 036226, "Report on the Study of Metiram (techn.), (ZNT Test Substance No.: 84/28), in the Ames Test" (BASF Aktiengesellschaft, Department Toxicology, Report # 85/020, 2/7/85). Metiram technical with 2.2% ETU added (DMSO solvent) was used in the Ames reverse mutation assay. Σαλμονελλα τψπηιμυριυμ strains TA98, TA100, TA1535, and TA1537 were treated at 0, 20, 100, 500, 2500, and 5000 µg/plate with and without activation (S9 fraction from Aroclor-induced male Fischer 344 rat and B6C3F1 mouse liver homogenates), at 0, 1, 10, 50, 100, 500, and 2500 µg/plate with activation, and at 0, 1, 10, 50, and 100 µg/plate without activation. There were no compound-related increases in reversion rates. The study is acceptable (J. Gee, 11/22/85).

217-010 038041, Jagannath et al., "Mouse Host-Mediated Assay of Metiram Tech K38/33A, Final Report", Litton Bionetics, Inc., Kensington, MD., Project # 20988, 06/85. Single oral gavages of metiram (technical K38/33A, unstated purity, 2.2% ETU added, 42.7% cleavable CS_2, suspended in 0.5% CMC) were given to 10 male CD-1 mice / dose at 0, 0.5, 1.67, or 5.0 g/kg. Thirty minutes later ip injections were given of histidine-dependent Σαλμονελλα τψπημυριυμ (TA-1530, Z 2X109 cells / animal). Three hours later the mice were sacrificed and samples of peritoneal fluid were plated to determine either total bacteria recovery (complete medium) or reversion rate to histidine-independent growth (minimal medium). No adverse effect was indicated by the lack of a treatment-related increase in revertant rate. The study is unacceptable and not upgradeable because there was no analysis of dosing material, no demonstration of test-material exposure, insensitivity of the assay, and only one tester strain was used (H. Green and S. Morris 04/03/91).

217-010 038043, H. P. Gelbke and R. Jäckh, "Report on a point mutation test carried out on CHO cells (HGPRT locus) with the test substance metiram (techn. purity)", BASF, Department of Toxicology, Ludwigshafen, Germany, report # 85/238, 07/31/85. The forward mutation rate of the HGPRT locus was analyzed by measuring the cloning efficiency of Chinese Hamster Ovary cells in the presence of thioguanine after exposure to metiram (unstated purity, lot # CH K 38/33 A, 2.2% ETU added, 42.7% cleavable CS_2) with or without metabolic activation (S9 fraction of Aroclor 1254 induced, male, Sprague-Dawley rat liver homogenate) at 0, 0.068, 0.100, 0.464, 0.681, 1.00, 4.64, or 6.81 µg/ml and with activation at 10.0, 46.4, 68.1, or 100 µg/ml. A **possible adverse effect** was indicated by treatment-related increases in 6-thioguanine resistant colonies after exposure with and without metabolic activation. The study was unacceptable because there was no GLP statement and no purity analysis. The study is not upgradeable because there was only 1 functional replicate per treatment level and the treated cells were improperly subcultured before selection (H. Green and S. Morris 04/15/91).

CHROMOSOME EFFECTS

217-010 038042, JL Ivett and CS Spicer, "Mutagenicity Evaluation of Metiram Technical K38/33A in an Iv citro Sister Chromatid Exchange Assay in Chinese Hamster Ovary (CHO) Cells, Final Report", Litton Bionetics, Inc., Kensington, MD., Project # 20990, March 1985. Metiram (technical K38/33A, unstated purity, 2.2% ETU added, 42.7% cleavable CS_2) was tested for sister chromatid exchange (SCE) in Chinese Hamster Ovary cells at 0, 40, 60, 80, or 100 µg/ml without metabolic activation and at 0, 125, 150, 175, or 200 µg/ml with S9 metabolic activation system from Aroclor 1254 induced Fischer 344 rat or B6C3F1 mouse liver homogenates. Adequacy of exposure was demonstrated by treatment-related cytotoxicity. The positive controls were adequate. No increase in SCE was reported with the rat activation system. A **possible adverse effect** was indicated by increased SCE without and with the mouse activation system. The study is unacceptable but possibly upgradeable with a statement of purity (H. Green and S. Morris, 04/04/91).

217-026 048606, JL Ivett and H Lebowitz, "Mutagenicity Evaluation of Metiram Technical K38/33A, in the Rat Bone Marrow Cytogenetic Assay, Amended Final Report", Litton Bionetics, Inc., Kensington, MD., Project # 22202, August, 1986. Metiram (technical K38/33A, unstated purity, suspended in 0.5% carboxymethylcellulose) was given by oral gavage to male Fischer 344 rats. Thirty rats / dose were given 0, 0.24, 0.80, or 2.40 g/kg to 30 and 10 rats / dose were sacrificed at 6, 24, or 48 hours. Ten rats / dose were given 5 consecutive daily doses of 0, 0.02, 0.10, or 0.20 g/kg and sacrificed 6 hours after the last dose. All rats were given 4 mg/kg colchicine, ip, 3 hours prior to sacrifice and their bone marrow cells were harvested, stained and Z 50 metaphase cells / rat were microscopically examined for chromosome aberrations. There were no treatment related increases in chromosome aberrations. No adverse was indicated. The study is unacceptable but possibly upgradeable with submission of adequate statement of purity, analysis of dosing material, clarification of sacrificed time point of positive controls, rationale for dose levels, and justification for using only males (H. Green and S. Morris, 04/19/91).

DNA DAMAGE

** 217-011 036224, "Evaluation of Metiram Tech. in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay, Final Report" (Litton Bionetics, Inc., Kensington, MD., Project # 20991, 7/5/84). Metiram Technical of unstated purity with 2.2% ETU added was used in an unscheduled DNA synthesis assay with triplicate, 18-19 hour exposures of adult male Fischer 344 rat hepatocytes at 0, 0.492, 1.23, 2.46, 4.92, 12.3, 24.6, 49.2, and 160 µg/ml. Cytotoxicity was seen at 160 µg/ml. No increase in unscheduled DNA synthesis was reported. The study was acceptable (J. Gee, 11/22/85).

217-010 038040, Alice S. Tu et al., "Evaluation of Metiram in the C3H-10T 1/2 Cell System for Transformation and Promotion Activities", Arthur D. Little, Inc., Cambridge, MA., Report # 54045 (1-5527), 6/18/85. Aqueous suspensions of metiram (unstated purity, 2.2% ETU added, 42.7% cleavable CS_2) were tested on cultured C3H-10T 1/2 mouse embryo fibroblasts. Treatment with 1.0 µg/ml of test material produced 80 to 100% decrease in plating efficiency. Exposure to 0, 0.10, 0.25, 0.50, 0.75, or 1.0 µg/ml (18 to 24 plates / concentration) produced no treatment-related increases in transformed foci. A **possible adverse** effect was indicated by increased numbers of transformed foci when a 24-hour treatment with 0.5 µg/ml MNNG was followed by a continuous exposure to 0.30 µg/ml of test material for approximately 5 weeks. The study is unacceptable but possibly upgradeable with submission of a statement of purity and trials using metabolic activation (H. Green and S. Morris, 04/01/91).

NEUROTOXICITY

Not required at this time.

SUPPLEMENTAL

217-003 006413, Brian Hunter et al., "Metiram Toxicity to Rats in Dietary Administration for 13 Weeks Followed by a 6 Week Withdrawal Period", BSF/197/77612, Huntington Research Centre, Cambridgeshire, England, 11/16/77. Metiram of unstated purity containing 2.2% ETU was fed in

the diets of 35 rats / sex / group at 0, 50, 100, 300, or 900 ppm for 13 weeks followed by a 6 week withdrawal. At the end of week 13, 5 rats / sex / group were injected iv with ^{131}I and 4 and 24 hour total plasma levels and plasma protein binding and total and protein-bound thyroid uptake of ^{131}I were measured. Marginally lower body weights and food intake were seen at 900 ppm. A **possible adverse effect** was indicated by decreased thyroid ^{131}I uptake at 50, 100, 300, 900 ppm; skeletal muscle lesions at 300, 900 ppm; lower serum T4 levels at 300, 900 ppm; and thyroid hyperplasia in males and hind limb paralysis in females at 900 ppm (NOEL < 50 ppm). The study is unacceptable and not upgradeable because of insufficient duration and a NOEL was not demonstrated. No worksheet was done (Morris 3/8/91).

Note: The finding of skeletal muscle lesions (doc. # 217-003, rec. # 006413) is consistent with those seen in the unacceptable combined chronic toxicity/oncogenicity study in rat (doc. # 217-015, rec. # 036234) and the thyroid effects are consistent with those seen in the chronic toxicity study in monkey (doc. # 217-006, rec. # 006416).

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